



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/SE90/00426 (22) International Filing Date: 15 June 1990 (15.06.90) (30) Priority data: 8902257-8 21 June 1989 (21.06.89) SE (71) Applicant (for all designated States except US): YTKEMISKA INSTITUTET [SE/SE]; Box 5607, S-114 86 Stockholm (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): SJÖSTRÖM, Brita [SE/SE]; Polhemsgatan 27 ^{III} , S-112 30 Stockholm (SE). KRONBERG, Bengt [SE/SE]; Elsa Brändströms gata 19, S-126 63 Hägersten (SE). CARLFORS, Johan [SE/SE]; Prästgårdsvägen 13C, S-752 30 Uppsala (SE). BLUTE, Irena [SE/SE]; Lojovägen 10, S-181 47 Lidköping (SE).		(74) Agent: AWAPATENT AB; Box 7045, S-103 94 Stockholm (SE). (81) Designated States: AT (European patent), AU, BE (European patent), BG, BR, CA, CH (European patent), DE (European patent)*, DK (European patent), ES (European patent), FI, FR (European patent), GB (European patent), HU, IT (European patent), JP, KP, KR, LU (European patent), NL (European patent), NO, RO, SE (European patent), SU, US. Published <i>With international search report.</i>
(54) Title: A PROCESS FOR THE PREPARATION OF DRUG PARTICLES (57) Abstract <p>A process for the preparation of submicron size, monodisperse drug-particles of a drug of low water-solubility by emulsifying an organic solution of the drug in an aqueous phase and then removing the organic solvent resulting in drug precipitation, containing the steps: a) emulsifying the organic solution in the presence of an emulsifier comprising a surfactant capable of adsorption on the surface of a precipitated drug-particle; b) removing the organic solvent from the suspension; and c) recovering the precipitated drug-particles from the aqueous phase or storing the same in the original aqueous phase.</p>		

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A process for the preparation of drug particles.

The present invention relates to a process for the preparation of submicron size, relatively monodisperse drug-particles of a drug of low water-solubility.

5 The size of water-insoluble drug-particles or such particles of a drug of low water-solubility is of considerable importance for the bioavailability of the drug. The rate of dissolution of the particles is directly proportional to their specific area and, accordingly, the size is critical
10 for the absorption and distribution of the drug in the tissue. Another argument for producing submicron particles is that the smaller particle size will allow alternative ways of administration of the drug substance. For pharmaceutical applications drug-particles of submicron size are therefore desirable. Such particles are, in accordance with conventional
15 techniques, produced by milling, a process which reduces the mean particle size to a few microns. However, the process produces a rather broad size-distribution thus resulting in illdefined dissolution kinetics. Such milling process frequently also results in contamination and degradation of the
20 drug.

 An alternative to such milling is to precipitate particles by crystallization. This is a more complex process which involves nucleation and growth kinetics but which is an
25 alternative that overcomes the particle size limitations of milling processing. However, also according to this alternative the difficult inherent in using crystallization is that of controlling the particle size and the size distribution to meet with the requirements. Crystallization is a subject to
30 several phenomena that aggravate the problem of controlling particle size. First, a crystal growth can uncontrollably change particle size and broaden the size distribution. Second, crystals formed may aggregate or agglomerate also resulting in uncontrolled size growth and distribution.

The present invention has for an object to provide a process for the preparation of small particles of water-insoluble drugs or drugs of low water-solubility while controlling size distribution to avoid widely varying particle sizes.

Another object of the invention is to provide a process for such drug particle manufacture which is highly reproducible and easily controlled.

Yet another object of the invention is to devise a process through which small drug particles can be produced which meet with the usual pharmaceutical requirements.

These and other objects of the invention will be clear from the following detail description. Accordingly, the invention resides in a process for the preparation of submicron size relatively monodisperse drug-particles of a drug of low water-solubility or a water-insoluble drug by emulsifying an organic solution of the drug in an aqueous phase and then removing the organic solvent resulting in drug precipitation. Such process comprises the following steps:

- a) emulsifying the organic solution in the presence of an emulsifier and if needed a protective colloid comprising a surfactant capable of adsorption on the surface of a precipitated drug particle;
- b) removing the organic solvent from the suspension; and
- c) recovering the precipitated drug particles from the aqueous phase or storing the same in the original aqueous phase.

Removal of the organic solvent from the suspension can take place in different ways. The following procedures are examples of such organic solvent removal:

the organic solvent can be removed by evaporation;
the organic solvent can be removed by washing through continuous renewal of the aqueous phase;

the organic solvent can be removed by washing away same through dialysis by contact with a pure aqueous phase;

the organic solvent can be removed by contacting the emulsion with an excess of aqueous phase to dissolve the or-

ganic solvent therein resulting in precipitation of the drug.

When removing the organic solvent by evaporation it may occur that water of the aqueous phase evaporates at the same time resulting in reduced water content of the emulsion. Such evaporation of water can be compensated for by adding further quantities of aqueous phase to the emulsion during evaporation of the organic solvent.

The different possibilities of controlling the drop diameter of the emulsion, and the drop size of the emulsion can be maintained within relatively broad range, such as between about 0.1 and about 20 mm. The size of the drops of the emulsion can be controlled by varying the supply of mechanic energy, by varying the concentration of surfactant and by varying the ratio between organic solvent and aqueous phase in the emulsion. The concentration of surfactant can for practical reasons be molarly related to the molar concentration of the drug.

The surfactant used is subject to several requirements as to its function. Thus, it shall operate satisfactorily as an emulsifying agent, i.e. it shall result in the formation of a stable emulsion. It is possible to use a protective colloid in combination with the surfactant to improve the stability of the emulsion. The basic requirement according to the invention is to use a surfactant which is capable of adsorption on the surface of a precipitated drug-particle. By using such surfactants a controlled and reproducible precipitation of small drug-particles takes place and the particle size distribution will be maintained within fairly narrow ranges.

Furthermore, the surfactant preferably inhibits aggregation and agglomeration of the particles and should advantageously be capable of inhibiting crystal growth. Such crystal growth is partly eliminated in view of reduced surface energy when the surfactant is adsorbed on the surface of the crystals.

It is preferred to use a protective colloid to stabilize the suspension. Said colloid can be synthetic, semi-synthetic or can be constituted by a polysaccharide or a pro-

tein. Parts of the protective colloid must be water-soluble to give colloidal stability. Micell formation in solution should be avoided but this is not necessary if the solubilizing capacity thereof on the crystal-forming substance is low. Possible incorporation of the tenside and/or the protective colloid in the crystal structure of the particle is permissible.

It is important to note that the process of the present invention does not involve any reaction in the system and that the process is not based on so called micro-emulsions.

It is advantageous in the process of the invention that no or very little mass transportation takes place between the drops of the emulsion and this requires a certain minimum concentration of drug in said drops.

Below there are given non-limiting examples of drugs, organic solvents and surfactants suitable for use in the process of the invention.

DRUGS

As water-insoluble drugs or drugs of low water-solubility the following are of interest.

Examples of drugs whose bioavailability has been increased as a result of particle size reduction

A, vitamin	Medroxyprogesterone acetate
4-Acetamidophenyl, 2,2,2-tri-	Nitrofurantoin
-chloroethyl carbonate	Phenobarbital
Aspirin	Phenacetin
Bishydroxycoumarin	Procaine penicillin
Chloramphenicol	Reserpine
Cyheptamide	Spironolactone
Digoxin	Sulfadiazine
Fluocinolone acetonide	Sulfasoxazole
Griseofulvin	Sulfur
p-Hydroxypropiofenone	Tolbutamide

Drugs with potential bioequivalency problems.

	Acetazolamide	Para-aminosalicylic acid
	Acetyldigitoxin	Para-methadione
	Alseroxylon	Perphenazine
5	Aminophyllin	Phenacetamide
	Aminosalicylic acid	Phensuximide
	Bendroflumethiazide	Phenylaminosalicylate
	Benzthiazide	Phenytoin
	Betamethasone	Phytonadione
10	Bishydroxycoumarin	Polythiazide
	Chlorambucil	Prednisolone
	Chlorodiazepoxide	Primidone
	Chlorothiazide	Probenecid
	Chloropromazine	Procainamide
15	Cortisone acetate	Prochlorperazine
	Deserpidine	Promazine
	Dexamethasone	Promethazine
	Dichlorophenamide	Propylthiouracil
	Dienestrol	Pyrimethamine
20	Diethylstilbestrol	Quinethiazide
	Dyphylline	Quinidine
	Ethinyl estradiol	Rauwolfia serpentina
	Ethosuximide	Rescinnamine
	Ethotoin	Reserpine
25	Ethoxzolamide	Salicylazosulfapyridine
	Fludrocortisone	Sodium sulfoxone
	Fluphenazine	Spironolactone
	Fluprednisolone	Sulfadiazine
	Hydralazine	Sulfadimethoxine
30	Hydrochlorothiazide	Sulfamerazine
	Hydroflumethiazide	Sulfaphenazole
	Imipramine	Sulfasomidine
	Isoproterenol	Sulfasoxazole
	Liothyronine	Theophylline
35	Menadione	Thioridazine
	Mephenytoin	Tolbutamide

cont.

	Methazolamide	Triamcinolone
	Methyclothiazide	Trichlormethiazide
	Methylprednisolone	Triethyl melamine
5	Methyltestosterone	Trifluoperazine
	Nitrofurantoin	Triflupromazine
	Oxtriphylline	Trimeprazine
		Trimethadione
		Uracil mustard
10		Warfarin

ORGANIC SOLVENTS

Among suitable organic solvents for use in the emulsion the following can be mentioned.

Any organic solvent that is a liquid and is poorly soluble in water. A prerequisite is that the solvent must be removed to concentrations that are acceptable from a toxicological point of view.

Examples:

- linear, branched or cyclic alkanes with carbon number of 5 or higher; e.g. n-pentane, n-heptane and higher linear alkanes; 2,2-dimethyl butane or 2,2,4-trimethyl pentane; cyclopentane, cyclohexane, methylcyclohexane etc.
- linear, branched or cyclic alkenes with carbon number of 5 or higher; e.g. 2-pentene, cyclohexene, 1,3 cyclopentadiene or 2,3 dimethyl-1-pentene.
- linear, branched or cyclic alkynes with carbon number of 5 or higher; e.g. 2-pentyne or 4-methyl-2-pentyne.
- aromatic hydrocarbons; e.g. toluene, ethylbenzene.
- completely or partially halogenated hydrocarbons; e.g. dichlormetan, chloroform, chlorobenzene, chlorobenzoic acid etc.
- ethers; e.g. diethylether etc.
- esters; e.g. ethylacetate, 9-Octadecenoic acid, ethyl ester, ethyl oleate, tetradecanoic acid 1-methylethyl ester, etc.

- ketones; e.g. cyclohexanone, 2-pentanone etc.
- mono-, di- or tri-glycerides; e.g. synthetic glycerol triacetate, glycerolmonolinolein etc., and native oils: almond oil, cotton seed oil, corn oil, olive oil, peanut oil, sesame oil, soybean oil etc.
- alcohols; e.g. benzenemethanol pentanol, hexanol etc.
- aldehydes; e.g. hexanol,
- acids; e.g. hexanoic acid,
- amines; e.g. 1-aminoheptane,
- nitriles; e.g. amylcyanide,
- silicones, linear or cyclic; e.g. octamethyltetrasiloxane or hexamethyldisiloxane,
- or any combination of these derivatives; e.g. 1-chloro-3-ethylhexane,
- or any combination of these solvents.

SURFACTANTS

Surfactants or groups of surfactants meeting with the requirements as indicated above are for example:

- Glyceryl monoalkylate; diacetyl tartaric acid esters of mono- and diglycerides of edible fats or oils, or edible fat-forming fatty acids; mono- and diglycerides of edible fats or oils, or edible fatforming acids; monosodium phosphate derivatives of mono- and diglycerides of edible fats or oils, or edible fat-forming fatty acids; glycerol ester of wood rosin; alcy l monoglyceridyl citrate;
- succistearin (stearoyl propylene glycol hydrogen succinate); dioctyl sodium sulfosuccinate; lecithins (pure and technical qualities); hydroxylated lecithins; methyl glucoside-coconut oil ester; sodium alcy l sulfate; potassium alcy l sulfate; sodium or potassium mono- and dimethyl naphthalene sulfonates; sodium or potassium alcy l fumarate; acetylated monogly-

cerides; succinylated monoglycerides; monoglyceride citrate; ethoxylated mono- and diglycerides; ethoxylated sorbitan esters; sorbitan monostearate; sorbitan esters of fatty acids; calcium alcyloyl-2-lactylate; sodium alcyloyl-2-lactylate; 5 potassium alcyloyl-2-lactylate; lactic esters of fatty acids; lactylated fatty acid esters of glycerol and propylene glycol; glyceryl-lacto esters of fatty acids; ethoxylated alcyyl phenols and alcohols; polyglycerol esters of fatty acids; propylene glycol mono- and diesters of fats and fatty 10 acids; sucrose fatty acid esters; fatty acids; salts of fatty acids; synthetic fatty alcohols; poloxamers; meroxapol; poloxamine; "pluradot", or any combination of these.

PROTECTIVE COLLOIDS

15 In the following there are also given examples of preferred protective colloids:

Gums: e.g. acacia, agar, carrageenan, guar, karaya, locust bean, pectin, propylene glycol alginate, sodium alginate, tragacanth, xanthan, gum arabicum.

20 Cellulosics: e.g. carboxymethylcellulose, sodium, microcrystalline cellulose and carboxymethylcellulose, sodium, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl methylcellulose, cellulose acetate phtalate, methylcellulose, ethyl hydroxyethyl cellulose, methocel.

25 Clays: e.g. Bentonite (colloidal aluminum silicate), colloidal magnesium aluminum silicate (hectorite), colloidal magnesium aluminum silicate (attapulgit), magnesium silicate (sepiolite).

30 Miscellaneous: e.g. Carbomer NF, gelatin, polyethylene glycols, polypropylene glycols and copolymers thereof, lecithins, Carbopol 934, Veegum, polyacrylic acid, polymethacrylic acid, polyacrylic acid-CO-acrylamide, polyvinylpyrrolidone, polyvinylalcohol with varying degree of hydrolysis.

35 Proteins: e.g. albumine, gelatine, casein or any combination of these

The invention will be further described in the following by non-limiting examples. In these examples the drug model used is cholesteryl acetate, which substance is useful for illustrating the problem solved by the present invention.

5 In these examples reference is made to the appended drawings, wherein:

Fig. 1 illustrates the effect of the method of emulsification on the particle size;

10 Fig. 2 illustrates a diagram on the size of emulsion droplets and the cholesterol acetate particles as a function of the concentration of cholesterol acetate in toluene; and

Fig. 3 illustrates the size of the emulsion droplets and the cholesterol acetate particles as a function of the concentration of surfactant.

15

EXAMPLE 1

An emulsion of cholesteryl acetate dissolved in toluene and an aqueous phase containing ethoxylated nonylphenol ether as a surfactant is prepared in the following manner.
20 The drug model substance, cholesteryl acetate, is dissolved in toluene. The solution is emulsified with an aqueous phase containing ethoxylated nonylphenol ether as a surfactant to form an oil-in-water-type emulsion.

25 The organic solvent, toluene, is then evaporated from the emulsion, whereby the drug model substance precipitates and the crystals are stabilized by the surfactant, said surfactant being adsorbed on the surface of the precipitated particles.

30 Using the emulsion ingredients indicated above a series of tests are made to establish the effect of the method of emulsification on the particle size, the influence of the concentration of the drug substance in toluene on the size of the particles and the influence of concentration of surfactant in the emulsion on the size of the emulsion droplets and
35 thus also on the size of the model drug-particles.

This illustration of different effects is made in relation to the appended drawings numbered 1 to 3 and related to the respective effects outlined above. In Fig. 1 the particles were obtained from emulsions which were prepared by vibration, and the particle sizes were measured by an electrozone sensing method. In Fig. 2 the emulsions were prepared by homogenization with a microfluidizer, and the particle sizes were measured by quasi-elastic light scattering. With regard to Fig. 3 the emulsions were prepared by homogenization with a microfluidizer.

Yet another alternative to control the emulsion droplet size is to vary the oil/water phase ratio.

EXAMPLE 2

This example illustrates the use of a surfactant capable of stabilizing the emulsion and suspension of cholesterol acetate and cyclohexane, respectively. The emulsion is homogenized in a microfluidizer. The oil/water phase ratio is 10/90, and the amount of surfactant is 5% by weight based on the weight of the oil phase. The surfactant used is a mixture of Tween 80 and Span 80 at a weight ratio of 1:9. Span 80 is a tradename for sorbitan monooleate and Tween 80 a tradename of POE-(20)-sorbitan monooleate.

The particle size in the suspension lies within the range of between about 80 nm and about 400 nm. The particle size is measured after 10 days and is found to be about constant.

EXAMPLE 3

Example 2 is repeated but using a mixture of Tween 20 and Span 80 (weight ratio 16:1) as a surfactant. Similar results are obtained.

EXAMPLE 4

Example 2 is repeated but using Tween 80 as a surfactant.

EXAMPLE 5

Example 2 is repeated but using DK ESTER F-160 (a sucrose ester) as a surfactant.

5

EXAMPLE 6

Example 2 is repeated but using Ovothin 170 (egg phospholipid) as a surfactant.

10

EXAMPLE 7

Example 2 is repeated but using Epikuran 145 (soybean lecithin) as a surfactant.

EXAMPLE 8

15

Example 2 is repeated but using Epikuran 200 SH (soybean lecithin) and the sodium salt of glycocholic acid (4:1) as a surfactant.

EXAMPLE 9

20

Example 2 is repeated but using Epikuran 200 SH and the sodium salt of taurocholic acid (4:1) as a surfactant.

EXAMPLE 10

25

Example 2 is repeated but using Ovothin 170 and the sodium salt of glycocholic acid (4:1) as a surfactant.

EXAMPLE 11

30

Example 2 is repeated but using Ovothin 170 and the sodium salt of taurocholic acid (4:1) as a surfactant.

EXAMPLE 12

Example 2 is repeated but using Triodan 55, polyglycerol esters of fatty acids as a surfactant.

35

EXAMPLE 13

Example 2 is repeated but using Acidan N-12, citric acid esters of monoglycerides as a surfactant.

EXAMPLE 14

Example 2 is repeated but using Epikuran 200 SH as a surfactant and polyvinylpyrrolidone as a protective colloid.

5 In the above Examples 4-14 results corresponding to those of Example 2 are obtained.

CLAIMS

1. A process for the preparation of submicron size, relatively monodisperse drug-particles of a drug of low water-solubility by emulsifying an organic solution of the drug in an aqueous phase and then removing the organic solvent resulting in drug precipitation, characterized by the steps:

- a) emulsifying the organic solution in the presence of an emulsifier, and if needed a protective colloid, comprising a surfactant capable of adsorption on the surface of a precipitated drug-particle;
- b) removing the organic solvent from the suspension; and
- c) recovering the precipitated drug-particles from the aqueous phase or storing the same in the original aqueous phase.

2. A process according to claim 1, characterized in that the organic solvent is removed by evaporation.

3. A process according to claim 1, characterized in that the organic solvent is removed by washing through continuous renewal of the aqueous phase.

4. A process according to claim 1, characterized in that the organic solvent is removed by washing away same through dialysis by contact with a pure aqueous phase.

5. A process according to claim 1, characterized in that the organic solvent is removed by contacting the emulsion with an excess of aqueous phase to dissolve the organic solvent therein resulting in precipitation of the drug.

6. A process according to claim 2, wherein aqueous phase is added during evaporation to compensate for co-evaporation of water from the aqueous phase.

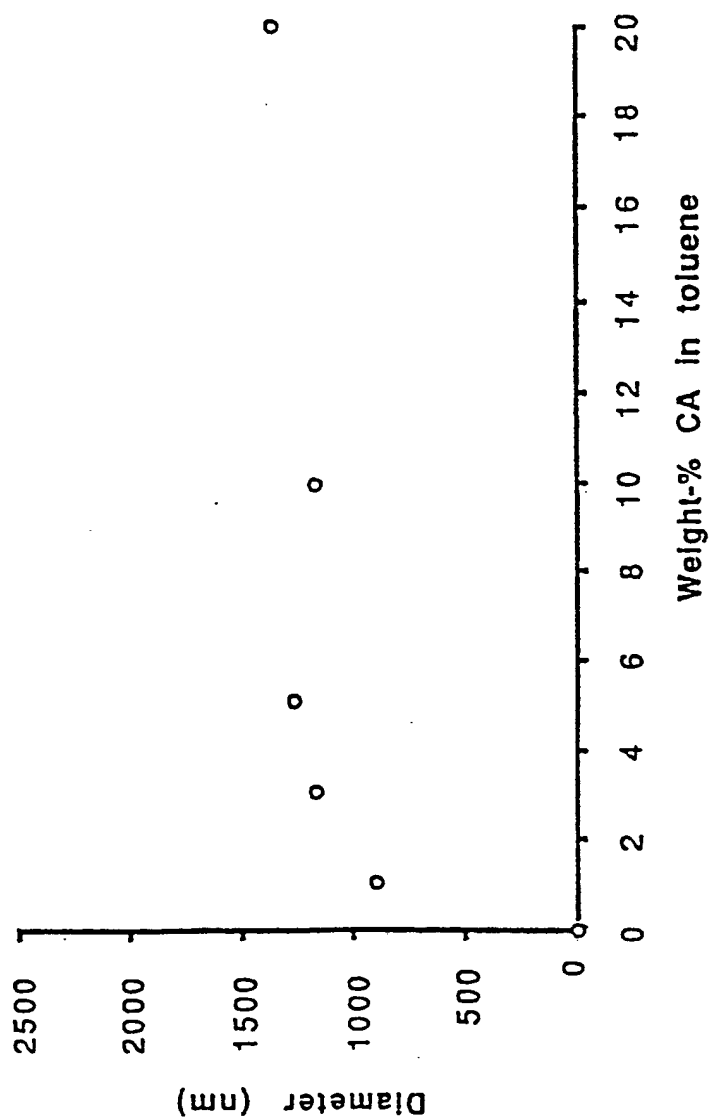
7. A process according to any preceding claim, wherein the drop diameter of the emulsion is controlled by the concentration of surfactant.

8. A process according to claim 7, wherein said concentration is related to the molar concentration of the drug.

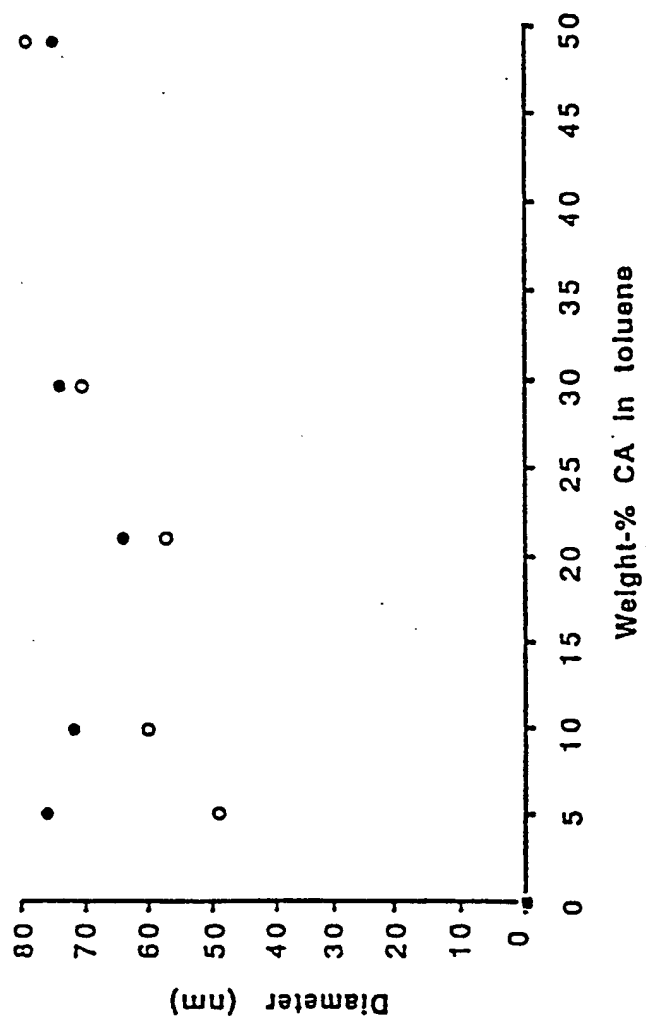
9. A process according to any preceding claim, wherein the surfactant is pharmaceutically acceptable.

10. Drug particles whenever prepared by the process of
any preceding claim.

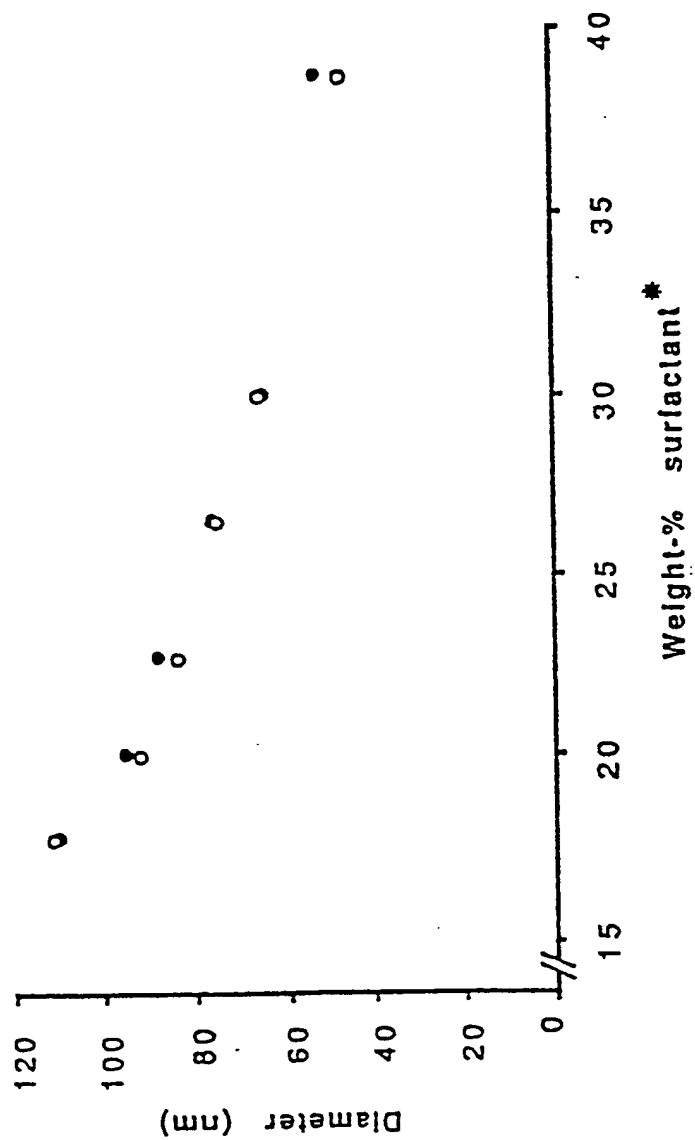
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*Calculated with respect to CA only.

INTERNATIONAL SEARCH REPORT

International Application No PCT/SE 90/00426

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC IPC5: A 61 K 9/10, 9/14, 9/50																	
II. FIELDS SEARCHED <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black;">Minimum Documentation Searched⁷</div> <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 25%; border-bottom: 1px solid black;">Classification System</td> <td style="border-bottom: 1px solid black;">Classification Symbols</td> </tr> <tr> <td style="height: 40px; vertical-align: bottom;">IPC5</td> <td style="vertical-align: bottom;">A 61 K; A 61 J; B 01 J</td> </tr> </table> <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched⁸</div> <p>SE,DK,FI,NO classes as above</p>			Classification System	Classification Symbols	IPC5	A 61 K; A 61 J; B 01 J											
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III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹ <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 10%;">Category[*]</th> <th style="width: 60%;">Citation of Document,¹¹ with indication, where appropriate, of the relevant passages¹²</th> <th style="width: 30%;">Relevant to Claim No.¹³</th> </tr> </thead> <tbody> <tr> <td style="text-align: center; vertical-align: top;">X</td> <td>US, A, 4826689 (M.R. VIOLANTO ET AL.) 2 May 1989, see column 2, line 60 - column 4, line 2; column 5, lines 7-36 --</td> <td style="text-align: center; vertical-align: top;">1,3,4,5, 9,10</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">X</td> <td>EP, A, 0169618 (STERILIZATION TECHNICAL SERVICES INC) 29 January 1986, see page 4, line 22 - page 5, line 19 --</td> <td style="text-align: center; vertical-align: top;">1,3-5,9- 10</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">A</td> <td>US, A, 3979520 (W. ROTHE ET AL.) 7 September 1976, see the whole document --</td> <td style="text-align: center; vertical-align: top;">1,2,6, 10</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">A</td> <td>DE, A, 2817453 (ROHNER AG PRÄTTELN) 31 October 1979, see page 7, line 7 - page 10, line 14 -- -----</td> <td style="text-align: center; vertical-align: top;">1-10</td> </tr> </tbody> </table>			Category [*]	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³	X	US, A, 4826689 (M.R. VIOLANTO ET AL.) 2 May 1989, see column 2, line 60 - column 4, line 2; column 5, lines 7-36 --	1,3,4,5, 9,10	X	EP, A, 0169618 (STERILIZATION TECHNICAL SERVICES INC) 29 January 1986, see page 4, line 22 - page 5, line 19 --	1,3-5,9- 10	A	US, A, 3979520 (W. ROTHE ET AL.) 7 September 1976, see the whole document --	1,2,6, 10	A	DE, A, 2817453 (ROHNER AG PRÄTTELN) 31 October 1979, see page 7, line 7 - page 10, line 14 -- -----	1-10
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<div style="display: flex; justify-content: space-between;"> <div style="width: 48%;"> <p>[*] Special categories of cited documents: ¹⁰</p> <p>^{"A"} document defining the general state of the art which is not considered to be of particular relevance</p> <p>^{"E"} earlier document but published on or after the international filing date</p> <p>^{"L"} document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>^{"O"} document referring to an oral disclosure, use, exhibition or other means</p> <p>^{"P"} document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 48%;"> <p>^{"T"} later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>^{"X"} document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>^{"Y"} document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>^{"&"} document member of the same patent family</p> </div> </div>																	
IV. CERTIFICATION <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; border-bottom: 1px solid black;">Date of the Actual Completion of the International Search</td> <td style="width: 50%; border-bottom: 1px solid black;">Date of Mailing of this International Search Report</td> </tr> <tr> <td style="border-bottom: 1px solid black;">12th September 1990</td> <td style="border-bottom: 1px solid black; text-align: center;">1990 -09- 17</td> </tr> <tr> <td style="border-bottom: 1px solid black;">International Searching Authority</td> <td style="border-bottom: 1px solid black;">Signature of Authorized Officer</td> </tr> <tr> <td style="text-align: center;">SWEDISH PATENT OFFICE</td> <td style="text-align: center;">Niklas Forstlund</td> </tr> </table>			Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	12th September 1990	1990 -09- 17	International Searching Authority	Signature of Authorized Officer	SWEDISH PATENT OFFICE	Niklas Forstlund							
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**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. PCT/SE 90/00426**

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the Swedish Patent Office EDP file on **90-08-02**.
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